Primary pulmonary myxoid sarcoma: A case report

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Abstract. Pulmonary myxoid sarcoma is an rare and poorly understood malignant neoplasm that primarily arises within the pulmonary tissue. Characterized by its distinctive histological features of myxoid stroma and spindle-shaped cells, this neoplasm poses significant diagnostic and therapeutic challenges due to its rarity and the non-specific nature of its clinical presentation. Current knowledge regarding the pathogenesis, optimal therapeutic strategies and prognostic factors for pulmonary myxoid sarcoma remains limited, primarily due to the scarcity of reported cases and comprehensive studies. The present study reports a case of pulmonary myxoid sarcoma. A 41-year-old male was admitted to the Jeonbuk National University Hospital due to a pulmonary mass in the left lower lobe discovered during a routine health check-up. A CT scan performed at our hospital revealed a nodule ~1 cm in size in the mediobasal segment of the left lower lobe, with relatively well-defined margins and significant enhancement. A wedge resection was performed for diagnosis and treatment, and frozen section examination showed a high likelihood of pleomorphic adenoma. The histological findings of the permanent section examination revealed an abundant myxoid matrix with embedded spindle, stellate and rounded/epithelioid cells arranged in a reticular pattern. The tumor cells exhibited mild to moderate cellular atypia, with rare mitotic figures. Immunohistochemistry showed positive staining for vimentin and negative findings for myoepithelial cell markers such as calponin, high-molecular weight cytokeratin and p63. The presence of the EWSR1-CREB1 fusion was confirmed through fluorescence in situ hybridization and reverse transcription-PCR analyses. Based on these findings, the nodule was diagnosed as pulmonary myxoid sarcoma.

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Introduction

Primary pulmonary myxoid sarcoma (PPMS) is a rare malignant tumor arising within the lung, originally described by Nicholson *et al* (1) in 1999. In 2011, Thway *et al* (2) introduced the term based on its distinctive genetic profile. A characteristic feature of PPMS is the EWSR1-CREB1 gene fusion, which aids in its identification and differentiation from other sarcomas. The World Health Organization formally recognized PPMS as a distinct interlobar tumor entity in 2015, marking its classification among rare pulmonary neoplasms (3). To date, fewer than 40 cases have been reported to the best of our knowledge (4).

Due to its scarcity, the understanding of PPMS clinical presentation, biological behavior and optimal management strategies remains limited. Histologically, PPMS is characterized by a unique myxoid stroma and spindle-shaped cells, which can resemble other soft tissue sarcomas and contribute to potential diagnostic challenges (5). The clinical presentation of PPMS is typically non-specific, and the lack of clear symptoms often results in incidental detection (5). Additionally, the pathogenesis of PPMS remains poorly understood, with few molecular studies exploring its underlying genetic alterations (2,6). However, recent advances, such as the identification of EWSR1 gene rearrangement through fluorescence *in situ* hybridization (FISH) testing, reverse transcription-PCR (RT-PCR) or sequencing, have begun to shed light on the molecular characteristics of this tumor.

The current study presents the case of a 41-year-old male diagnosed with PPMS that was initially suspected to be pleomorphic adenoma based on frozen section analysis. The diagnosis was confirmed through histological examination and immunohistochemical staining, along with FISH analysis revealing EWSR1 rearrangement. This case highlights the importance of increasing awareness and advancing diagnostic precision to better understand and manage this rare tumor.

Case report

A 41-year-old male was admitted to Jeonbuk National University Hospital (Jeonju, South Korea) in April 2024, following the incidental discovery of a mass in the left lower lobe during a routine health check-up. The patient had no significant past medical history, and his physical examination was otherwise unremarkable. A contrast-enhanced computed

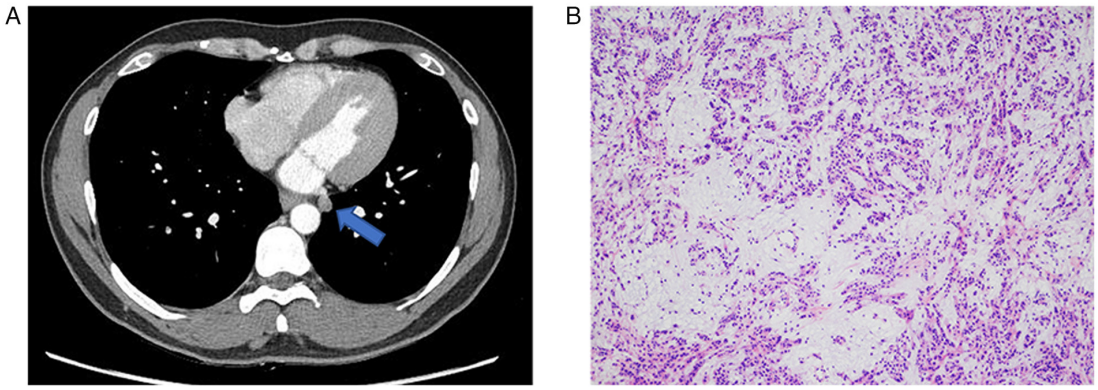

Figure 1. Radiological and intraoperative findings of the pulmonary nodule. (A) Contrast-enhanced computed tomography image showing a well-defined nodule ~1 cm in size located in the mediobasal segment of the left lower lobe. (B) Intraoperative frozen section analysis of the wedge-resected nodule showing abundant myxoid stroma and scattered spindle cells (hematoxylin and eosin stain; original magnification, x100).

tomography (CT) scan performed at Jeonbuk National University Hospital revealed a small pulmonary nodule, ~1 cm in size, located in the mediobasal segment of the left lower lobe (Fig. 1A). The nodule had relatively well-defined margins, though some areas appeared irregular, raising suspicion for a potentially malignant lesion.

Due to its deep-seated location, a percutaneous transthoracic needle biopsy was considered challenging. Therefore, to obtain a definitive diagnosis, the patient underwent a wedge resection of the left lower lobe mass. Intraoperative frozen section analysis was performed using standard intraoperative pathological procedures. Tissue samples were rapidly frozen at -20˚C using a cryostat. Sections were cut at a thickness of 5 μm and mounted on glass slides. Staining was performed with haematoxylin and eosin (H&E); slides were stained in haematoxylin at room temperature for 5 min, rinsed in water and counterstained with eosin at room temperature for 1 min. All sections were imaged using a light microscope. Frozen section analysis suggested a high likelihood of pleomorphic adenoma; however, the final diagnosis was deferred pending permanent histopathological analysis (Fig. 1B). For permanent histopathological analysis, tissue specimens were fixed in 10% neutral buffered formalin at room temperature for 24 h. After fixation, samples were processed and embedded in paraffin. Sections were cut at a thickness of 4 μm using a microtome and mounted on glass slides.

H&E staining was performed with haematoxylin staining for 3 minutes at room temperature, followed by eosin staining for 7 min utes at room temperature. All stained sections were examined usingnder a light microscope. Examination of the permanent sections revealed distinctive features, including an abundant myxoid matrix with embedded spindle, stellate and rounded/epithelioid cells arranged in a reticular pattern, exhibiting mild cellular atypia and rare mitotic figures. Notably, giant or bizarre tumor cells, which have been reported in some previous cases, were not observed in the present case (Fig. 2A and B).

Immunohistochemical (IHC) staining was performed to further aid in diagnosis. Staining was performed using an automated immunostainer (BenchMark ULTRA; Ventana Medical Systems, Inc.) according to the manufacturer's protocol. Tissue sections were fixed in 10% neutral buffered formalin at room temperature for 24 h, processed routinely, and embedded in paraffin. Sections were cut at a thickness of 4 μm and mounted on glass slides. All primary antibodies used were ready-to-use products provided by the manufacturer (Roche); therefore, no dilution was required. All staining steps, including deparaffinization, antigen retrieval, blocking, antibody incubation, and detection, were carried out automatically under pre-optimized and standardized conditions according to the manufacturer's instructions.

Hematoxylin was applied as a counterstain for 5 minutes at room temperature. All stained slides were examined using a light microscope. The tumor cells were positive for vimentin and epithelial membrane antigen but negative for myoepithelial cell markers, including calponin, high-molecular-weight cytokeratin and p63 (Fig. 2C-F). This pattern effectively ruled out pleomorphic adenoma and other myoepithelial tumors. Other markers, such as CD68, anaplastic lymphoma kinase (ALK), insulinoma-associated 1 (INSM1) and synaptophysin were negative. Given these histological and immunohistochemical findings, which aligned with characteristics of PPMS, the possibility of PPMS was considered.

To further confirm the diagnosis, fluorescence in situ hybridization (FISH) analysis was performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections. A commercially available break-apart probe targeting the *EWSR1* gene (Vysis LSI *EWSR1* Break Apart Rearrangement Probe; Abbott Pharmaceutical) was used in accordance with the manufacturer's protocol. This probe is specifically designed to detect *EWSR1* gene rearrangement but does not identify the specific fusion partner. All procedures, including hybridization and washing steps, were carried out in accordance with the manufacturer's instructions. Fluorescent signals were evaluated using a fluorescence microscope, and at ≥100 nuclei were assessed by a trained cytogeneticist. A result was considered positive when >15% of the examined nuclei demonstrated a split signal pattern, consistent with *EWSR1* rearrangement. In this case, the FISH analysis demonstrated the presence of an *EWSR1* gene rearrangement. Following this, RNA was extracted from the specimen to specifically verify the presence of the EWSR1-CREB1 fusion. Total RNA was extracted from FFPE tumor tissue using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions.

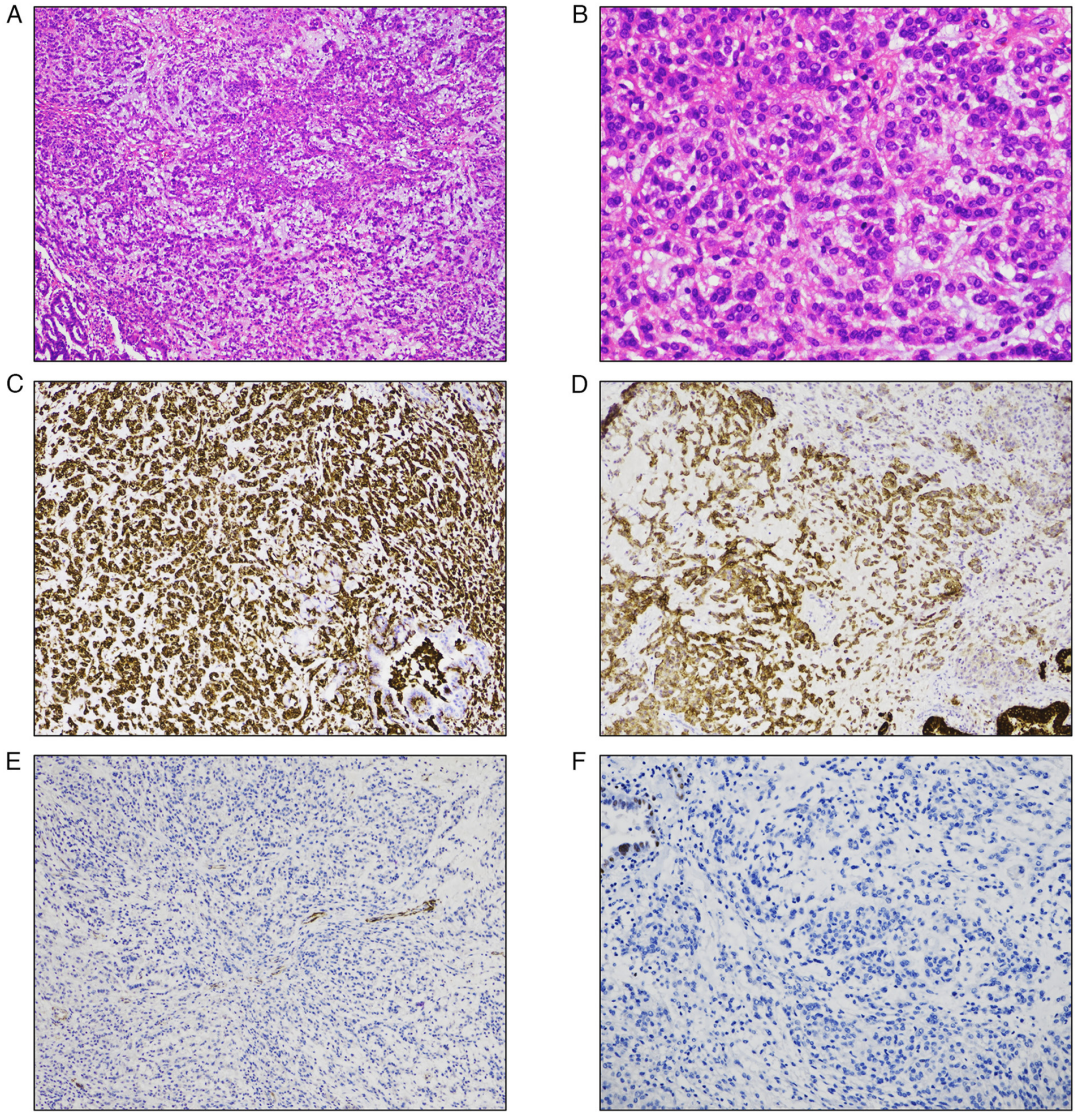

Figure 2. Histopathological and immunohistochemical findings of PPMS. (A) Lower-power view of the PPMS showing abundant myxoid stroma (arrows) with spindle and rounded/epithelioid shaped tumor cells exhibiting mild to moderate atypia (H&E stain; original magnification, x100). (B) Higher magnification of H&E staining highlighting the cellular morphology and mitotic activity (arrow) (original magnification, x400). (C-F) Tumor cells show positive staining for (C) vimentin (arrow) (original magnification, x100) and (D) epithelial membrane antigen (arrow) (original magnification, x100), while (E) negative for calponin (original magnification, x100) and (F) p63 (original magnification, x200). PPMS, primary pulmonary myxoid sarcoma; H&E, hematoxylin and eosin.

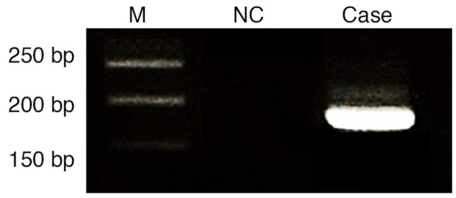

Figure 3. Detection of EWSR1-CREB1 fusion transcript using reverse transcription-PCR. Gel electrophoresis image showing a distinct PCR band corresponding to the EWSR1-CREB1 fusion transcript in the present case sample (Lane 3). Lane 1: DNA size markers; Lane 2: NC; Lane 3: Sample of present case (case). NC, negative control.

Reverse transcription was performed using the SuperScript™ IV First-Strand Synthesis System (Thermo Fisher Scientific, Inc.) following the manufacturer's standard protocol. PCR amplification was carried out using primers designed to target exon 7 of *EWSR1* (5'-TCCTACAGCCAAGCTCCAAGT C-3') and exon 7 of *CREB1* (5'-GTACCCCATCGGTACCAT TGT-3'). The PCR thermocycling conditions were as follows: initial denaturation at 95˚C for 5 min, followed by 35 cycles of denaturation at 95˚C for 30 sec, annealing at 60˚C for 30 sec and extension at 72˚C for 30 sec, with a final extension at 72˚C for 5 min. PCR products were analyzed by electrophoresis on a 2% agarose gel stained with ethidium bromide and visualized under UV illumination. A distinct band corresponding to the *EWSR1-CREB1* fusion transcript was observed (Fig. 3). Based on the histopathological findings, immunohistochemical profile and molecular analysis, a final diagnosis of primary pulmonary myxoid sarcoma was established. The patient did not receive adjuvant therapy postoperatively and has been monitored with imaging studies every 3 months. As of 10 months after surgery, there is no evidence of recurrence or metastasis. Due to the rarity of PPMS and its potential for misdiagnosis, further studies are needed to improve our understanding of its biological behavior, treatment responses, and prognostic factors.

Discussion

PPMS is a rare neoplasm, and as such, comprehensive epidemiological data are limited (5). The tumor most commonly affects middle-aged adults, with a median age of 49 years (range, 26-80 years) and a slight female predominance (5). Due to its rarity, precise incidence rates have not been established in population-based studies (5). The etiology of PPMS remains unclear, with no definitive causative factors identified. Unlike a number of other malignancies, PPMS has not been associated with smoking or linked to known inherited cancer predisposition syndromes (5). From a prognostic standpoint, surgical resection remains the mainstay of treatment, with ~90% of patients remaining disease-free following surgery (5). Nonetheless, a small subset of cases demonstrates metastatic progression, with documented spread to the lung, kidney or brain, and rare instances of lethal outcomes have been reported (5).

PPMS is a challenging tumor to diagnose, given its histological overlap with other soft tissue sarcomas and myoepithelial tumors. The present case exemplifies the diagnostic complexities associated with PPMS, which often lead to its initial misidentification. In the present patient, the intraoperative frozen section analysis suggested pleomorphic adenoma, a differential diagnosis often considered due to the myxoid nature of the lesion. However, definitive histopathology, immunohistochemistry and molecular testing ultimately confirmed the diagnosis of PPMS. The current case highlights the critical role of an integrated approach that combines histological, immunohistochemical and molecular analyses to achieve an accurate diagnosis.

The diagnostic process in the present case illustrates the challenges involved in diagnosing PPMS. The initial frozen section suggested pleomorphic adenoma, a diagnosis that was ultimately excluded based on the permanent histopathological and immunohistochemical findings. Histologically, PPMS is characterized by an abundant myxoid matrix with embedded tumor cells exhibiting spindle, stellate or rounded/epithelioid morphology, typically arranged in a reticular or cord-like pattern (5). The tumor cells display mild to moderate atypia, with low mitotic activity, though variability exists among cases (5). These features can closely resemble those of other soft tissue tumors, making accurate differentiation essential (5). Immunohistochemistry plays a crucial role in differentiating PPMS from other myoepithelial tumors (7). In the present case, the tumor cells stained positive for vimentin, a mesenchymal marker, but were negative for markers of myoepithelial differentiation, such as calponin, high-molecular-weight cytokeratin and p63, which helped rule out pleomorphic adenoma and similar entities.

A key diagnostic feature of PPMS is the EWSR1-CREB1 gene fusion, detectable by FISH or molecular techniques such as RT-PCR and sequencing (7). In the current case, the diagnosis was confirmed by identifying the EWSR1 rearrangement through FISH analysis, along with supportive immunohistochemical staining. Additionally, RT-PCR was conducted using primers designed to target exon 7 of EWSR1 and exon 7 of CREB1, and the amplification results confirmed the presence of the EWSR1-CREB1 fusion, further supporting the diagnosis. This highlights the crucial role of molecular testing in distinguishing PPMS from other sarcomas. The EWSR1-CREB1 fusion, although not entirely specific to PPMS, is highly characteristic and has been instrumental in defining this rare entity (8). A limitation of the present case report is the inability to confirm the EWSR1-CREB1 fusion using RNA sequencing. While the diagnosis was established through FISH and RT-PCR, RNA-sequencing would have provided a more definitive and comprehensive molecular validation of the fusion event.

However, several other tumors with similar histological characteristics also show EWSR1 rearrangements, which can complicate the diagnosis of PPMS (9,10). Extraskeletal myxoid chondrosarcoma (EMC) is one tumor with overlapping features, as it is characterized by multinodular growth and a rich myxoid matrix, similar to PPMS (11). It contains spindle-shaped to ovoid cells embedded in cords within the matrix. EMC is characterized by the presence of an EWSR1-NR4A3 fusion (11). Therefore, testing solely for EWSR1 rearrangement may not reliably distinguish EMC from PPMS. Immunohistochemical staining can aid in differentiating these two entities. EMC may show positive staining for neuroendocrine markers such as INSM1 and synaptophysin, reflecting a neural differentiation profile not typically seen in PPMS. By contrast, PPMS generally does not express INSM1 or synaptophysin, which serves as an important clue in distinguishing it from EMC (12). Angiomatoid fibrous histiocytoma (AFH) is another tumor with overlapping histological features, including a myxoid stroma and spindle cell morphology (13). Similar to PPMS, AFH can harbor EWSR1 rearrangements, most commonly resulting in EWSR1-CREB1 or EWSR1-ATF1 fusions, which can complicate the differential diagnosis (13). Immunohistochemistry offers additional diagnostic insight, as AFH often shows positive staining for markers such as CD68 and ALK, which are typically absent in PPMS (14). These immunohistochemical differences provide important clues for distinguishing AFH from PPMS. In the present case, immunohistochemical staining demonstrated negative results for synaptophysin, INSM1, CD68 and ALK. These findings further support the diagnosis of PPMS.

The treatment of PPMS poses significant challenges due to its rarity and limited clinical data. Due to the lack of established treatment guidelines, management is largely based on case reports and small case series. Surgical resection is generally considered the primary treatment for PPMS, especially for localized tumors, as complete resection offers the best chance for prolonged survival (6). In cases where the tumor is confined to the lung, lobectomy or wedge resection with negative margins is often pursued to achieve local control and reduce the risk of recurrence (4,15). For patients with inoperable or metastatic PPMS, systemic therapies, such as chemotherapy, may be considered, although the response rates in PPMS are not well documented (7). Sarcoma-oriented chemotherapy regimens, including agents such as doxorubicin and ifosfamide, have been used in some cases, but their efficacy remains uncertain (2,16). Due to the slow growth of PPMS in some patients, close surveillance may be preferred in select cases where aggressive treatment may not provide significant benefit (6). Emerging molecular insights into PPMS, particularly the identification of EWSR1-CREB1 fusions, may pave the way for targeted therapies in the future (6). While no targeted therapies specific to PPMS are available, identifying

molecular characteristics could open possibilities for the development of novel therapies aimed at these fusion proteins. Future research and collaboration among institutions will be essential to improve understanding of the biology of PPMS and to establish more standardized treatment protocols for this rare tumor.

In conclusion, the present case highlights the critical role of comprehensive diagnostic techniques, including histological, immunohistochemical and molecular approaches, in identifying PPMS. Increased awareness of PPMS among clinicians and pathologists is essential for avoiding misdiagnosis, given its resemblance to other myxoid neoplasms. Further research and accumulation of case data are necessary to enhance our understanding of PPMS and establish standardized treatment protocols, improving patient outcomes for this rare malignancy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JHK and KMK conceptualized the study and wrote the original manuscript. KMK searched the literature and obtained case-related data. KMK and JHK analyzed data and relevant literature. KMK reviewed and edited the final draft. KMK and JHK confirm the authenticity of all the raw data. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB no. 2024-09-008) and was conducted according to the Declaration of Helsinki.

Patient consent for publication

The patient provide written informed consent for the publication of his images.

Competing interests

The authors declare that they have no competing interests.

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